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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/310,685	05/04/1999	JONATHAN ROBERT LAMB	674525-2001	9186

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EXAMINER
DECLOUX, AMY M

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/310,685	Applicant(s) Lamb
	Examiner DeCloux, Amy	Art Unit 1644

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *12/4/01 and 1/3/02*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *7-25, 27-29, and 32-41* is/are pending in the applica

4a) Of the above, claim(s) *7-25, 32, 40, and 41* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-29 and 33-39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☒ Interview Summary (PTO-413) Paper No(s). 17

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Applicant's amendment and certified priority documents filed 12/4/01 (Paper No. 15), are acknowledged. Accordingly, Claims 30 and 31 have been canceled.

2. Said amendment makes reference to a response by applicant mailed 11-14-01, which the office has no record of. In a phone interview, Applicant said that the amendment, filed 12/4/01 (Paper No. 15) superseded the missing response by applicant mailed 11-14-01 (see attached interview summary). However because Applicant's amendment, filed 12/4/01, was faxed to the office on 12-4-01, which is after the expiration of the period for reply set in the restriction requirement mailed 10-23-01, a one month extension of time has been charged to Deposit Account No. 50-0320. Applicant's amendment, filed 12/4/01, authorizes charging any fee occasioned by said amendment. Said fee may be refunded if applicant presents a return receipt postcard from the USPTO indicating that the missing paper was mailed or received by the USPTO by 11-23-01.

Said amendment also has attached six studies applicant states were carried out by Applicants or Applicant's assignee. However, said studies will not be considered since it is not clear what relationship they have with the instant application. Applicant is requested to clarify.

3. Claims 7-25, 27-29 and 32-41 are pending.

4. Applicant's election with traverse of Group I, claims 27-31 and 33-41, (now claims 27-29 and 33-41) in Paper No. 15, filed 12-4-01, is acknowledged. The traversal is on the ground(s) that the present claims represent a web of knowledge and a continuity of effort that merits examination in a single application. Applicant also notes that MPEP 808.02 states restriction is not required unless one of the following appears: 1. separate classification. However, the examiner notes that in the restriction requirement mailed 10-23-01, Group I has been classified in class 514, subclass 2, a classification distinct from the remaining groups. Applicant further contends that a search of group I will necessarily involve a search of the non-elected groups which should therefore be rejoined to elected group I. This is not found persuasive because though the searches of the elected and non-elected groups may overlap, they are not co-extensive, for the reasons delineated in said restriction requirement, and as such would require an undue search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's amendment, filed 12/4/01 (Paper No. 15) contained a request for an interview regarding the restriction requirement prior to the issuance of a first office action. However, upon talking with the attorney of record Thomas Kowalski (see

attached interview summary), the attorney requested discussing the merits of the application before the first office action, which the examiner declined, and the attorney did not discuss the restriction requirement.

5. Claims 7-25, 32, **and 40-41** are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

It is noted that claims **40 and 41** were amended in Applicant's amendment, filed 12/4/01 (Paper No. 15). Before amendment, Claims 40-41 were originally grouped with the elected invention of Group I. However, since claims 40-41 now depend from claim 32 which is a non-elected invention, said claims are not being considered as part of the elected invention.

6. This application does not contain an Abstract of the Disclosure as required by *37 C.F.R. § 1.72(b).* An Abstract on a separate sheet is required.

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. as follows:

This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required. See MPEP 201.11.

The instant application filed 5-4-99 is a CIP of GB97/03058 filed 11/06/97, published as WO 98/20142 on 5-14-98, as indicated in the first line of the instant specification and in applicant's oath.

8. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in Great Britain on 11/7/1996, 7/24/1997, 9/11/1997 and 11/06/1997. A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

Acknowledgment is made of the certified copies of U.K. application Nos. 9719350.2, 9715674.9, 9623236.8 and PCT/GB97/03058, said copies having been received at the USPTO on 1-3-2002.

9. The disclosure is objected to because of the following minor informalities:

A) There appears to be a typographical error on page 12, line 14, "or" should perhaps be substituted for "on".

B) The last line of page 10 appears to have been repeated on the first line of page 11.

10. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 27-29, 33-37 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 27-29, 33-37 and 39 are drawn to a method of treating T-cell mediated disease or infection comprising administering a medicant comprised of a Notch ligand and encompass fragments, derivatives and analogues of Serrate or Delta, as specifically recited in claims 29 and 39.

The instant specification discloses on pages 10-12, that the notch ligands are preferably delta or serrate family members proteins or polypeptides or derivatives thereof, and include fragments thereof and derivatives of such fragments, and also includes the protein product of Delta, Serrate, Deltex and Enhancer of split genes as well as other members of this gene family identifiable by virtue of their gene sequences that hybridize to, or have homology with Notch Delta or Serrate proteins, or the ability of their genes to display phenotypic interactions.

The instant specification discloses on page 12 that the term variant and the term derivative, each includes any substitution of, variation of, modification of, replacement of, deletion of, or addition of one (or more) amino acid residues, providing that the resultant protein or polypeptide possesses the capability of modulating notch-notch ligand interactions. The instant specification also discloses on page 12 that the term "analog" includes any peptidomimetic that is a chemical compound that possesses the capability of modulating Notch-Notch ligand interactions in a similar manner to the parent polypeptide and include compounds that may agonize or antagonize the expression or activity of notch-protein or Notch ligand.

However, the instant specification does not describe a method comprising administering a medicant comprised of a notch ligand, except for the notch ligands of full length delta and full length serrate. Further, the instant specification does not describe a single method comprising administering a medicant comprised of a notch ligand wherein said ligand is a fragment, derivative, or an analog of any notch ligand including the recited notch ligands of Serrate or Delta.

In view of the disclosed broad definition of notch ligand that encompasses any of a number of known and unknown notch ligands, and in view of Artavanis-Tsakonas et al's teaching that Notch is a multifunctional receptor, (Science (1995) Vol 268:225-232, see entire article, especially the first sentence of page 229), there is insufficient written description in the instant specification to allow one of skill in the art to distinguish between the genus of notch ligands that interact with notch and effect T cells, compared to the genus of notch ligands which may not effect T cell activity.

Without a description of the structural basis for the biological interaction of T cells with notch ligands, known and unknown, it is not clear how one would visualize a notch ligand (except for full length delta or full length serrate) which could be administered in a method of treating T-cell mediated disease or infection. Similarly, neither is it clear how one would visualize a fragment or derivative of a notch ligand such as Serrate or Delta, which could be administered in a method of treating T-cell mediated disease or infection, especially in view of Ish-Horowicz et al's teachings(U.S. Patent 6,004,924)(1999) that derivatives, including but not limited to fragments and analogs, of serrate proteins can be either inhibitory or can retain one or more of the functions of full length wild type Serrate Protein (see entire patent, especially Section 5.6 in columns 19-20). Further there is no disclosure of a single species of the genus of analogs which as described on page 13 of the instant specification can be either agonistic or antagonistic of a notch protein or notch ligand.

Without a further description of the structural basis for the interaction of the T cells with a notch ligand, one of ordinary skill could not establish the boundaries of the genus of a medicant comprised of a notch ligand based only on the disclosure of full length Serrate and Delta, nor of the genus of a medicant comprised of a fragment of Serrate or delta, nor of the genus of a medicant comprised of a derivative of Serrate or Delta, nor of the genus of a medicant comprised of an analog of Serrate or Delta, wherein said genus would be administered in a method for treating a T-cell mediated disease or infection as claimed instantly. It is noted that though the claimed invention is directed to polypeptides and not cDNA, the principle of the following still holds for said polypeptides: a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

Therefore, only a method for treating a T-cell mediated disease or infection comprising administering a medicant comprised of the notch ligands consisting of full length Serrate and Delta, but not the full breadth of the instant claims, meets the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st

"Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 27-29 and 33-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention without an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858iF2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the level of predictability in the art, the state of the prior art, the amount of experimentation required to make or use the invention based on the content of the disclosure, the amount of guidance and direction presented, and the existence of working examples.

Claims 27-29 and 33-39 are drawn to a method of treating T-cell mediated disease or infection comprising administering a medicant comprised of a Notch ligand. The instant claims encompass fragments, derivatives and analogues of the notch ligand Serrate or Delta, as specifically recited in claims 29 and 39, and encompass a wide range of disease including allergy, autoimmunity graft rejection tumor induced aberrations to the T cell system and infectious diseases including those caused by plasmodium, helminths, cytomegalovirus, hepatitis, measles and Pseudomonas.

However, the specification does not enable one of skill in the art regarding a method for treating a T-cell mediated disease or infection comprising administering a notch ligand. The instant specification provides insufficient guidance and direction regarding the treatment of any disease comprising the administration of any medicant comprising any notch ligand or any notch ligand fragment, derivative and/or analog.

The instant specification discloses on page 3 and Example 1 shows that notch, delta and serrate are expressed in the peripheral immune system of the mouse, serrate being expressed on a subpopulation of antigen presenting cells and Delta's being expressed in a subset of T cells, though it is not clear from the instant disclosure what those subsets are. The instant specification also discloses in Example 4 and 10 shows that primed lymph node cells show reduced antigen specific proliferation when stimulated by irradiated T cell hybridomas transfected with full length Delta than T cell hybridomas transfected with vector alone, and also discloses in example 6 that lymph node cells from mice injected with said hybridomas and immunized with allergen showed reduced proliferation and Il-2 secretion 7 days later in vitro when incubated with said allergen. Example 5 shows that naive mice immunized with HDDM-peptide-pulsed dendritic cells (Dcs) transfected with full length Serrate, produce 10 fold fewer

recoverable LN cells, and that mice immunized with DCs and full length Serrate produce Lymph node cells that fail to proliferate or secrete IL-2. Similar results were disclosed using T cell clone reactive with an influenza peptide in examples 7 and 8. The instant specification also discloses in examples 11 and 12 that Delta is expressed on T cells during the induction of tolerance.

However, though these examples demonstrate a suppressive effect of full length serrate and full length Delta on T cell priming of naive cells and stimulation of primed T cells in response to specific antigens, it is not clear from the instant disclosure how these results enable one of skill to practice a method of treating any T-cell mediated disease or infection as recited in the instant claims, since no T cell mediated diseases or infections were disclosed to be treated. The instant specification provides insufficient guidance and direction regarding the T cells that mediate any of the broad range of the recited T-cell mediated diseases and infections, nor how any of the broadly recited notch ligands, upon administration, would be effective in treating said T-cell mediated diseases and infections, because the effectiveness of a method of treatment stems from the total immune response. This guidance is especially needed in view of the unclear nature of which notch receptors and which notch ligands are expressed on which lymphoid cells (such as antigen presenting cells, NK cells, T cell subsets and/or which other immune cells), as evidenced by the instant specification's disclosure on page 3 that the expression pattern of the notch family of receptors and their ligands in the normal peripheral adult immune system has not been previously described, and by Jaleco et al.'s teaching (Meeting Abstract (2001) Blood 98 (11): Part 2, page 117b) that the notch ligands delta and jagged can mediate differential effects of Notch signaling on B cells, T/NK cells, and CD4+/CD8+ cells, and by Janeway's teaching (Immunobiology, Fourth Edition, Garland Press, 1999, page 246) that notch protein overexpressed in thymocytes directs them to the CD8 lineage and may inhibit the pathway to CD4 T cells. In re Fisher, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the disclosed broad definition of notch ligand that encompasses any of a number of known and unknown notch ligands, and in view of Artavanis-Tsakonas et al's teaching that Notch is a multifunctional receptor, (Science (1995) Vol 268:225-232, see entire article, especially the first sentence of page 229), there is insufficient guidance and direction in the instant specification to allow one of skill in the art to predict which notch ligands interact with notch and effect T cells, and predict those that don't. Without a description of the structural basis for the biological interaction of T cells with notch ligands, known and unknown, there is insufficient guidance and direction in the instant specification to allow one of skill in the art to predict which fragment or derivative of a notch ligand such as Serrate or Delta, could be administered in a method of treating T-cell mediated disease or infection, especially in view of Ish-Horowicz et al's teachings(U.S. Patent 6,004,924)(1999) that derivatives, including but not limited to fragments and analogs, of serrate proteins can be either inhibitory or can retain one or more of the functions of full length wild type Serrate Protein (see entire

patent, especially Section 5.6 in columns 19-20), and the disclosure on page 13 of the instant specification that analogs can be either agonistic or antagonistic of a notch protein or notch ligand.

Therefore it would require undue experimentation for one of skill in the art to predict the efficacy of the administration of a medicant comprised of any notch ligand, including full length Serrate or Delta, or fragments or derivatives or analogs thereof, for the treatment of any T- cell mediated disease or disorder in view of the the insufficient guidance and direction regarding the effect of administration any notch ligand, including full length Serrate or Delta, on the activity of all the cells that make up the sum total of the immune response to a T cell mediated disease or infection. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

14. Claim 28 is rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 28 is indefinite in its recitation of the phrase " such as" in line 3. The term "such as" in claim 28 is a relative term which renders the claim indefinite. The term "such as" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 28 recites the broad recitation of infectious diseases, and the claim also recites several pathogens that cause infectious diseases, which is the narrower statement of the range/limitation.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 25,2002
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